



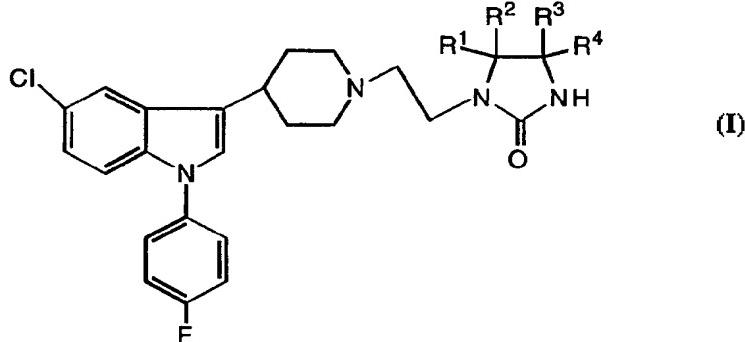
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(21) International Application Number: PCT/DK94/00407		(74) Agent: MEIDAHL PETERSEN, John; H. Lundbeck A/S, Patent Dept., Ottiliavej 9, DK-2500 Copenhagen-Valby (DK).	
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(71) Applicant (for all designated States except US): H. LUNDBECK A/S [DK/DK]; Ottiliavej 9, DK-2500 Copenhagen-Valby (DK).			
(72) Inventors; and (75) Inventors/Applicants (for US only): PERREGAARD, Jens, Kristian [DK/DK]; Thyrasvej 22, DK-3630 Jaegerspris (DK). MOLTZEN, Ejner, Knud [DK/DK]; Howitzvej 46, DK-2000 Frederiksberg C (DK). ANDERSEN, Kim [DK/DK]; Minervavej 11, DK-2610 Rodovre (DK). PEDERSEN, Henrik [DK/DK]; Mellemvangen 63, DK-2700 Broenshøj (DK). BØGESØ, Klaus, Peter [DK/DK]; Hørsholm Park 16, DK-2970 Hørsholm (DK). PERNET, Andre [US/US]; 2580 Telegraph Road, Bannockburn, IL 60015 (US). BOPP, Barbara [US/US]; 307 E. Blodgett, Lake Bluff, IL 60044 (US). MULFORD, Darcy [US/US]; 107 Chestnut Circle, Lindenhurst, IL 60046 (US). SAKAMOTO, Kiyoshi [JP/JP]; 26-16, Akashiadai 3-chome, Sanda, Hyogo 669-13 (JP).			

(54) Title: PHENYLINDOLE COMPOUNDS

(57) Abstract

Phenylindole compound having general formula (I), wherein R¹-R⁴ are independently hydrogen, deuterium, halogen, alkyl, aryl, hydroxy, alkoxy, aryloxy, alkylthio and arylthio; or R¹ and R² and/or R³ and R⁴ constitute an oxo or thioxo group; or R¹ and R² and/or R³ and R⁴, respectively, are joined together to form a 3-8 membered spiro ring; are non-cataleptogenic 5-HT₂ receptor antagonists *in vivo* and show in a model indicative of antipsychotic effect. Thus the compounds may be useful in the treatment of psychosis, depression, negative symptoms of schizophrenia, hypertension or extrapyramidal side effects induced by antipsychotic drugs.



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PHENYL INDOLE COMPOUNDS

Field of invention

- 5 The present invention is concerned with a class of novel phenylindole compounds related to the atypical neuroleptic sertindole (1-[2-[4-[5-chloro-1-(4-fluorophenyl)-
1*H*-indol-3-yl]piperidin-1-yl]ethyl]-2-imidazolidinone), however being substituted in
the 4- and/or 5-position of the imidazolidinone ring. Said compounds or a salt or pro-
drug thereof are useful as antipsychotics, antidepressants, antihypertensives and-
10 /or in the treatment of extrapyramidal side effects induced by antipsychotic drugs
and negative symptoms of schizophrenia.

Background of the invention

- 15 US patent No 4,710,500 corresponding to EP 200,322 B discloses in general
optionally 5-substituted 1-aryl-3-(4-piperidyl)-, 1-aryl-3-(1-piperazinyl)- or 1-aryl-3-
(1,2,3,6-tetrahydro-4-pyridyl)indole derivatives having hydrogen or alkyl, alkenyl or
certain heterocycle-lower alkyl substituents at the nitrogen atom in the piperidyl,
piperazinyl or tetrahydropyridyl group.

20

- Most of the compounds were shown to be potent and long-lasting centrally acting
dopamine antagonists *in vivo*, and accordingly to be useful in the treatment of psy-
chooses, and all the compounds were proven to be strong centrally acting 5-HT₂ re-
ceptor antagonists *in vivo* indicating effects in the treatment of depression, extrapy-
25 ramidal side effects induced by antipsychotic drugs and negative symptoms of schi-
zophrenia. The antipsychotic activity of one compound, i.e. the atypical neuroleptic
compound sertindole (recommended INN name), 1-[2-[4-[5-chloro-1-(4-fluorophe-
nyl)-1*H*-indol-3-yl]piperidin-1-yl]ethyl]-2-imidazolidinone, is described in US patent
No 5,112,838 corresponding to EP 392,959A.

30

In our International Patent Application Publ. No. WO 92/00070 a subclass of the 3-
(4-piperidyl) compounds, including sertindole, were found to show anxiolytic activi-
ty. Furthermore, said 3-(4-piperidyl) compounds have been reported to be useful

in the treatment of hypertension, drug abuse and cognitive disorders (International Patent Publications Nos. WO 92/15301, WO 92/15302 and WO 92/15303).

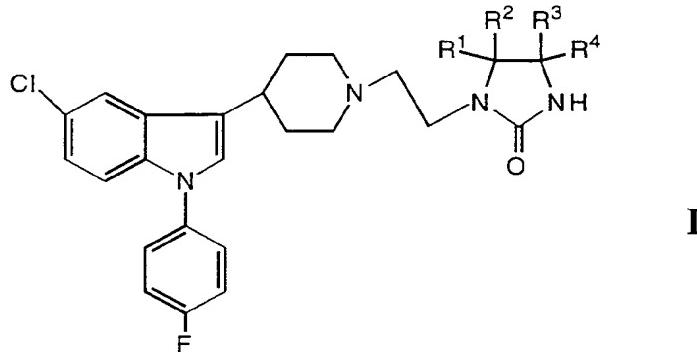
Metabolism studies have shown that a major circulating metabolite of the antipsychotic compound sertindole exists in humans. It is believed that prevention of the formation of said major metabolite might be advantageous.

Accordingly, the object of the invention is to provide novel drugs having a similar pharmacological profile to that of sertindole, in which drugs, however, the formation 10 of said metabolite is either delayed or prevented.

Summary of the invention

It has now been found that said major circulating metabolite of sertindole is the compound 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidin-1-yl]ethyl]-1,3-dihydroimidazol-2-one which is structurally identical to sertindole except for the double bond in the 1,3-dihydroimidazol-2-one ring. Furthermore, a class of novel phenyl-indole compounds related to sertindole, wherein the metabolic transformation of the imidazolidinone ring to a 1,3-dihydroimidazol-2-one ring is delayed or blocked, 20 have been found to show a similar pharmacological profile to that of sertindole.

Accordingly, the present invention relates to novel compounds having general Formula I



25 wherein R¹ - R⁴ are independently selected from the group consisting of hydrogen, deuterium, halogen, C₁₋₆ alkyl, cycloalkyl, cycloalkyl-C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, aryl, hydroxy, C₁₋₆ alkoxy, cycloalkyloxy, cycloalkyl-C₁₋₆ alkyloxy, aryl-C₁₋₆ alkyloxy,

aryloxy, C₁₋₆ alkylthio, cycloalkylthio, cycloalkyl-C₁₋₆ alkylthio, aryl-C₁₋₆ alkylthio and arylthio, with the proviso that all 4 substituents cannot be hydrogen; or at least one pair of substituents (R¹, R² or R³, R⁴) constitutes an oxo group or a thioxo group and, if only one oxo or thioxo group is present, the other two substituents are selected from the above group defined for R¹ - R⁴, with the proviso that they may not both be hydrogen; or R¹ and R² and/or R³ and R⁴, respectively, are joined together to form a 3-8 membered spiro ring optionally containing one oxygen or sulfur atom in the ring; or a prodrug or acid addition salt thereof.

10

In another aspect the invention relates to a method for the preparation of the novel compounds of Formula I.

15 In yet another aspect the invention relates to a pharmaceutical composition comprising a novel compound of Formula I together with a suitable pharmaceutically acceptable carrier or diluent.

20 In yet another aspect the invention relates to the use of the compounds of Formula I for preparing a pharmaceutical composition for treatment of psychosis, depression, negative symptoms of schizophrenia, hypertension or extrapyramidal side effects induced by antipsychotic drugs.

25 The compounds of the invention have been found to show a pharmacological profile similar to that of sertindole, whereas they are not liable to or less liable to transformation of the imidazolidinone ring into a 1,3-dihydroimidazol-2-one ring, which transformation takes place with respect to sertindole. The pharmacological profile of the compounds of the invention indicates that they are useful in the treatment of the above mentioned disorders.

30 **Detailed Description of the invention**

Some of the compounds of general Formula I may exist as optical isomers thereof, and such optical isomers are also embraced by the invention.

In general Formula I halogen means fluoro, chloro, bromo or iodo.

The term cycloalkyl designates a carbocyclic ring having 3-8 carbon atoms, preferably 3-6 carbon atoms, inclusive, or a bicyclic or tricyclic carbonring such as adamanyl.

The terms C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, etc. designate such branched or unbranched groups having from one to six carbon atoms inclusive, preferably from 10 one to four carbon atoms. Exemplary of such groups are methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2-methyl-1-propyl, methoxy, ethoxy, 1-propoxy, methylthio, ethylthio, 1-propylthio, 2-propylthio, methylsulfonyl, ethylsulfonyl, or the like.

15 The term aryl is intended to mean a carbocyclic or heterocyclic aromatic group optionally comprising one or more substituents independently selected from hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy, lower alkylthio, lower alkyl- or di-alkylamino, cyano, trifluoromethyl, and trifluoromethylthio. Exemplary of such aryl groups are phenyl, thienyl and furanyl.

20

The pharmaceutically acceptable acid addition salts of the compounds used in the invention are salts formed with non-toxic organic or inorganic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, embonic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanesulfonic, acetic, 25 propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraco-nic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromo-theophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

30

Prodrugs of the compounds of the invention may be analogous to the prodrugs of sertindole disclosed in our International Patent Application WO 92/06089, or they may be esters of C₁ - C₁₈ carboxylic acids formed with possible hydroxy groups on

the imidazolidinone ring.

- In a preferred embodiment of the invention R¹ - R⁴ are individually selected from the group consisting of hydrogen, deuterium, C₁₋₆ alkyl, hydroxy and C₁₋₆ alkoxy; or
- 5 one or both pair of substituents (R¹, R² or R³, R⁴) constitute an oxo group or R¹ and R² and/or R³ and R⁴, respectively are linked to form a 3-8 membered spiro ring.

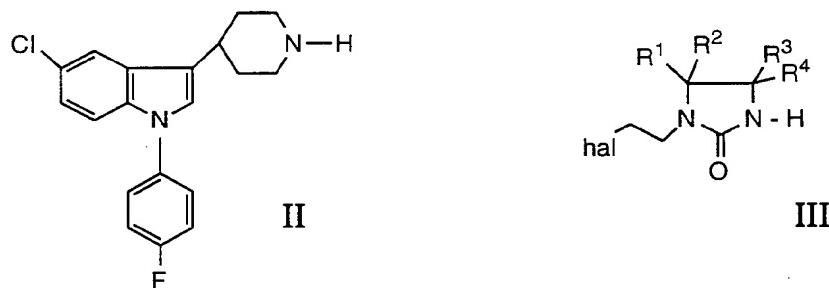
Preferably, both substituents of at least one pair of substituents (R¹, R² or R³, R⁴) are different from hydrogen or constitute together an oxo group.

10

According to the invention the novel compounds of formula I, are prepared by a method comprising:

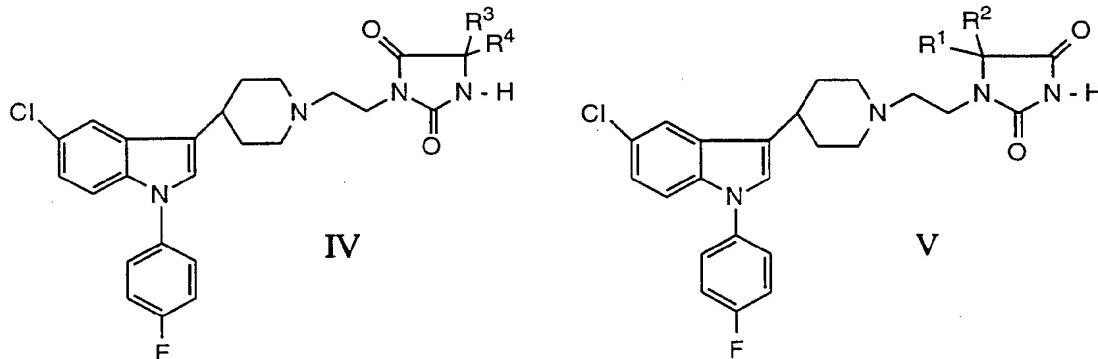
- a) reacting the 1-unsubstituted piperidine II with a compound of formula III:

15



wherein R¹ - R⁴ are as previously defined, and "hal" is chloro, bromo, or iodo;

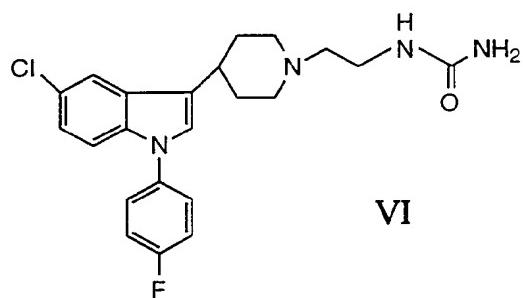
- b) reducing an oxo compound of Formula IV or V to a corresponding hydroxy or
20 methylene derivative:



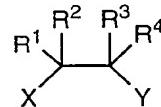
wherein R¹ - R⁴ are as previously defined;

c) reacting an urea derivative VI with a bifunctional group VII, whereby this group is inserted to form the ethylene bridge of compound I:

5



VI

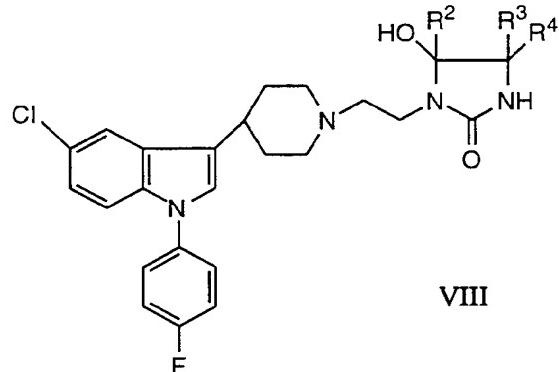


VII

wherein R¹ - R⁴ are as previously defined, and X and Y are chlorine, bromine, iodine, C₁₋₆ alkoxy or hydroxy;

d) reacting a compound of Formula VIII with an alcohol of Formula R^{1'}OH:

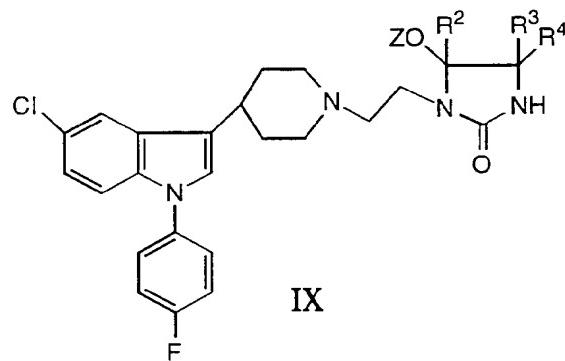
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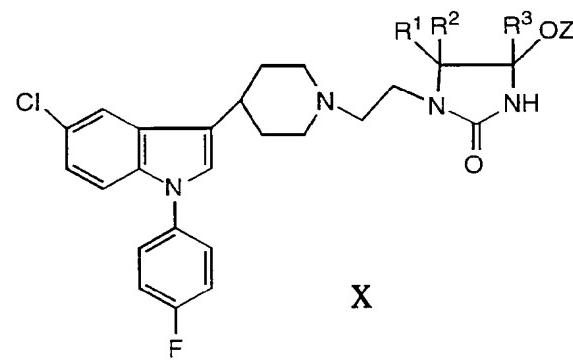
VIII

wherein R² - R⁴ are as previously defined, and R^{1'} is C₁₋₆ alkyl, cycloalkyl, cycloalkyl-C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, or aryl;

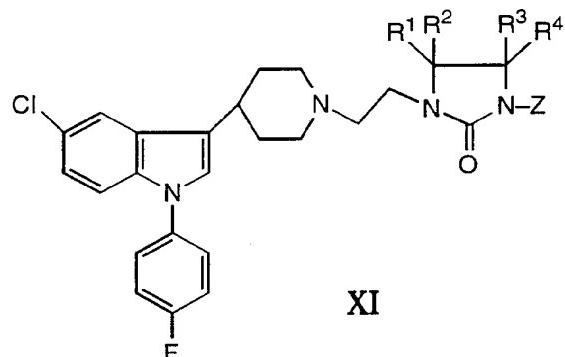
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IX



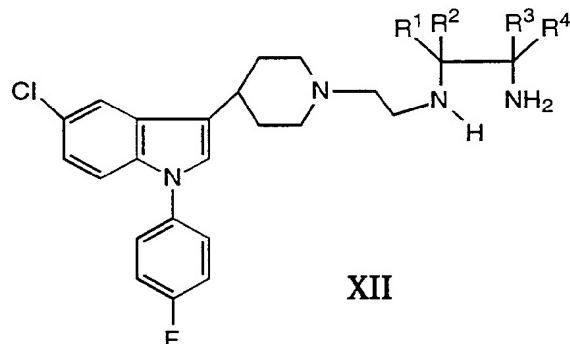
X



wherein R¹ - R⁴ are as previously defined, and the protecting group Z is trialkylsilyl, benzyl, acyl, or another protecting group removable under non-acidic conditions; or

5

f) ringclosure reaction of an ethylene diamine derivative of Formula XII:



wherein R¹ - R⁴ are as previously defined, using urea, phosgene, dialkyl carbonate or carbamates to incorporate a carbonyl group to form the heterocyclic ring of

10 Formula I.

Preparation of the intermediate II is reported in Perregaard et al. *J.Med.Chem.*, 1992, 35, 1092-1101, and preparation of the intermediate III appears from the Examples. The alkylation of II with III is generally performed at elevated 15 temperatures in an inert solvent such as acetone, methyl isobutyl ketone or N-methyl-2-pyrrolidone in the presence of a base such as e.g. potassium carbonate.

The oxo compounds IV and V are conveniently reduced to the corresponding hydroxy compounds using LiAlH₄, AlH₃, B₂H₆ or a BH₃ complex under mild 20 conditions, such as cooling in inert solvents as e.g. diethyl ether or dry tetrahydrofuran. Preparation of the oxo compounds is described in the Examples.

Compounds with bifunctional groups VII are e.g. oxalic acid derivatives such as oxalyl chloride or oxalic acid esters or glyoxylic acid derivatives. The reaction of these derivatives with VI is conveniently performed under acidic or neutral
5 conditions.

The reaction of a compound of Formula VIII with an alcohol R¹'OH is conveniently performed in an inert solvent, or with the alcohol as solvent at room temperature or at elevated temperature.
10

Protecting groups Z in Formulas IX-XI are removed by methods such as cleavage of a trialkylsilyl protection group with tetraalkylammonium fluoride in an inert solvent or by mild aqueous hydrolysis. Benzyl groups are removed by catalytic hydrogenation using e.g. Pd as a catalyst. Carboxylic acid esters are hydrolyzed
15 under mild neutral or basic conditions well-known to a chemist skilled in the art. The intermediates of Formulas IX-XI may be obtained by methods conventional in the art.

Compounds of Formula XII are prepared according to the methods described in
20 International Patent Application No. WO 92/15302, Chem. Abstr. 117 (1992) 247029 or as shown in the Experimental Section. The reaction of XII with urea, dialkyl carbonates or carbamates is generally performed at high temperatures (100-200 °C) either with the neat components or in an inert aprotic solvent such as N,N-dimethylformamide, N-methyl-2-pyrrolidinone or hexamethylphosphoric triamide.
25 Phosgene as the carbonyl precursor is used at low temperatures in inert solvents such as toluene, tetrahydrofuran, diethyl ether optionally in the presence of a base, such as triethylamine or potassium carbonate.

The acid addition salts of the compounds of the invention are easily prepared by
30 methods well known in the art. The base is reacted with either the calculated amount of organic or inorganic acid in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling, or reacted with an excess of the acid in an aqueous immiscible solvent such as ethyl

ether or chloroform, with the desired salt separating directly. These salts may also be prepared by the classical method of double decomposition of appropriate salts.

The compounds of general Formula I, the prodrugs thereof and the pharmaceutically acceptable acid addition salts thereof may be administered in any suitable way, e.g. orally or parenterally, and the compounds may be presented in any suitable form for such administration, e.g. in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. The prodrugs may conveniently be administered as depot preparations for injection, dissolved in proper oils.

10

An effective daily dose of the a compound of general Formula I or a pharmaceutically acceptable salt thereof is from 10 µg/kg to 10 mg/kg body weight.

Examples

15

In the following the invention is further illustrated by way of examples which may in no way be construed as limiting for the invention.

All melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. ^1H NMR spectra were recorded at 250 MHz on a Bruker AC 250 spectrometer. Deuterated chloroform (99,8 %D) or dimethylsulfoxide (99,9 %D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals : s=singlet, d=doublet, t=triplet, q=quartet, h=heptet, dd=double doublet, dt=double triplet, dq=double quartet, tt=triplet of triplets, m=multiplet.

EXAMPLE 1 (method b)

1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidin-1-yl]ethyl]-5-hydroxy-imidazolidin-2-one, 1

1-(2-chloroethyl)imidazolidin-2,5-dione, 1a

To a suspension of glycine (49 g) in water (750 ml) was added sodium hydroxide

(39 g) and the mixture was subsequently cooled to 0 °C. 2-Chloroethylisocyanate (75 g) was added dropwise at 0-10 °C during 1/2 hour. The mixture was stirred for another hour at 10 °C. pH was adjusted to 1 by addition of concentrated hydrochloric acid. The precipitated glycine derivative was filtered off, washed with water and finally dried *in vacuo*. Yield: 106 g, mp: 146-149 °C. All of the glycine derivative thus obtained was suspended in concentrated hydrochloric acid (520 ml) and heated to reflux for 20 minutes. The acidic solvent was evaporated *in vacuo*. The remaining crude product was dissolved in dichloromethane and dried (anh.MgSO₄). Dichloromethane was evaporated, and the crystalline product was recrystallized from ethyl acetate, yielding 62 g of the title compound **1a**. Mp: 112-114 °C.

1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-5-hydroxy-imidazolidin-2-one, 1

A suspension of 5-chloro-1-(4-fluorophenyl)-3-(4-piperidinyl)-1*H*-indole (45 g) (prepared as described in *J.Med.Chem.* **1992**, *35*, 1092-1101), 1-(2-chloroethyl)imidazolidin-2,5-dione, **1a** (45 g), potassium carbonate (40 g), and potassium iodide (10 g) was refluxed for 5 hours in methyl isobutyl ketone (MIBK) (400 ml). The mixture was filtered while still hot, and MIBK was subsequently evaporated *in vacuo*. The remaining crude product was purified by column chromatography on silica gel using a mixture of ethyl acetate/ethanol/triethylamine (90:10:4) as eluent. The resulting pure hydantoin derivative was recrystallized from ethyl acetate. Yield: 21 g, mp: 165-166 °C. The thus obtained hydantoin derivative (7 g) was dissolved in dry THF (250 ml). A solution of LiAlH₄ (0.7 g) in dry THF (50 ml) was added dropwise at 5-10 °C. The mixture was finally stirred for 5 hours at room temperature. After cooling to 0 °C aqueous NaOH (1.2 ml) and water (3 ml) were cautiously added. Inorganic salts were filtered off, the solvents evaporated *in vacuo* and the remaining crude solid recrystallized from ethyl acetate. Yield 5.3 g of the title compound **1**, mp: 174-175 °C. ¹H NMR (δ , CDCl₃): 8.45 (broad s, 1H), 7.60 (d, 1H), 7.40-7.30 (m, 3H), 7.25-7.10 (m, 3H), 7.05 (s, 1H), 5.25 (broad s, 1H), 5.15 (d, 1H), 3.95 (broad d, 1H), 3.60-3.50 (m, 1H), 3.25 (broad d, 2H), 3.05 (t, 2H), 2.85 (tt, 1H), 2.75 (broad t, 1H), 2.55-2.35 (m, 2H), 2.20-2.05 (m, 3H), 1.90-1.75 (m, 2H).

EXAMPLE 2 (method e)

1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidin-1-yl]ethyl]-4-hydroxy-imidazolidin-2-one, **2**

- 5 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidin-1-yl]ethyl]-imidazolidin-2,4-dione , **2a**

Potassium cyanate (30 g) was suspended in dichloromethane (400 ml), and trifluoroacetic acid (50 ml) was added dropwise at 5-8 °C. A solution of 5-chloro-3-[1-(N-cyanomethyl-2-aminoethyl)-4-piperidyl]-1-(4-fluorophenyl)-1*H*-indole (50 g)

- 10 (International Patent Application No. WO 92/15302, Chem. Abstr. 117 (1992) 247029) in dichloromethane (200 ml) was added with cooling, and the mixture was stirred overnight at room temperature. The reaction mixture was washed twice with cold dilute sodium hydroxide solution, and the organic phase was dried (anh. MgSO₄), and the solvent was evaporated *in vacuo* yielding 53 g of crude urea derivative, which was refluxed in ethanol (700 ml) and concentrated hydrochloric acid (50 ml) for one hour. After cooling to room temperature the mixture was filtered yielding 33 g of the hydrochloric salt of the title compound **2a**. The salt was dissolved in a mixture of methanol (150 ml) and triethylamine (33 ml), and after a few minutes the free base crystallized, yielding 24 g of the title compound **2a**. Mp: 208-210 °C.

20

1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidin-1-yl]ethyl]-3-[*N*-(*tert*-butyldimethylsilyl)]imidazolidin-2,4-dione, **2b**

- A solution of **2a** (8.24 g) in dichloromethane (500 ml), tetrahydrofuran (150 ml) and triethylamine (10 ml) was heated to reflux. A solution of *tert*-butyldimethylsilyl chloride (3.35 g) in dichloromethane (100 ml) was added during 15 minutes. After 2 hours another portion of *tert*-butyldimethylsilyl chloride (3 g) in dichloromethane (50 ml) and triethylamine (10 ml) was added, and after another 2 hours a similar portion of *tert*-butyldimethylsilyl chloride was added. The mixture was refluxed overnight and was then evaporated *in vacuo*. The residue was dissolved in dichloromethane and was washed with water and saturated brine. The organic phase was dried (anh. MgSO₄), and was evaporated *in vacuo* to give 12.6 g of the crude title compound **2b** as an oil.

1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-4-hydroxy-3-[N-(tert-butyldimethylsilyl)]imidazolidin-2-one, 2c

To a solution of **2b** (16.2 g) in ether (1 l) was added lithium aluminium hydride (1.62 g) in portions during 40 minutes at room temperature. The mixture was stirred for 5 another 20 minutes. The reaction was quenched with water and concentrated sodium hydroxide and the mixture was filtered and evaporated *in vacuo*. Purification by column chromatography (silica gel, eluent: triethylamine/ethanol/ethyl acetate 4:4:100) gave 10.1 g of the title compound **2c**. Mp: 154-155 °C.

10 **1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-4-hydroxy-imidazolidin-2-one, 2**

A solution of tetrabutylammonium fluoride, trihydrat (1.5 g) in tetrahydrofuran (600 ml) was cooled to -53 °C. A solution of **2c** (1.5 g) in tetrahydrofuran (300 ml) was added during 15 minutes at -53 °C. The mixture was stirred at -53 °C for another 90 15 minutes, and was then cooled to -70 °C and poured on saturated sodium chloride solution at 10 °C. The mixture was extracted with dichloromethane, and the organic phase was washed with saturated brine, dried (anh. MgSO₄) and evaporated *in vacuo* at room temperature. The residue was redissolved in ethyl acetate and was shaken with saturated brine, and then concentrated aqueous ammonia was added 20 to pH 12. The organic phase was dried (anh. MgSO₄) and evaporated *in vacuo* at room temperature. Purification by column chromatography (silica gel, eluent: triethylamine/ethanol/ethyl acetate 15:15:70) gave the title compound, which was crystallized from ethyl acetate to yield 0.294 g of **2**. Mp.: 176-178 °C.

1H NMR (δ , DMSO-*d*₆) 7.70 (d, 1H), 7.62-7.58 (m, 2H), 7.47 (s, 1H), 7.47-7.34 (m, 25 3H), 7.16 (dd, 1H), 7.00 (s, 1H), 5.82 (d, 1H), 5.02 (t, 1H), 3.56 (dd, 1H), 3.28-3.17 (m, 2H), 3.13 (dd, 1H) 2.99 (broad d, 2H), 2.80 (tt, 1H), 2.42 (t, 2H), 2.11 (broad t, 2H), 1.95 (broad d, 2H), 1.69 (broad q, 2H).

EXAMPLE 3 (method d)

30 **1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-5-methoxy-imidazolidin-2-one, fumarate 3**

A solution of 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-

5-hydroxyimidazolidin-2-one (compound **1**) (3 g) in methanol (1000 ml) was refluxed for 24 hours. Excess methanol was evaporated *in vacuo*. The remaining crude product was dissolved in acetone, and fumaric acid (0.75 g) was added. Upon heating the title compound **3** crystallized as the fumarate salt.. Yield: 2.7 g.

5 mp: 126-127 °C. ¹H NMR (δ , DMSO-d₆): 7.75 (d, 1H), 7.65-7.55 (m, 2H), 7.50 (s, 1H), 7.50-7.30 (m, 3H), 7.15 (dd, 1H), 6.65 (broad s, 1H), 6.60 (s, 2H), 5.10 (d, 1H), 3.60-3.45 (m, 1H), 3.40-3.15 (m, 5H), 3.15 (s, 3H), 2.95 (broad t, 1H), 2.80 (t, 2H), 2.55 (t, 2H), 2.05 (broad d, 2H), 2.00-1.80 (m, 2H).

10 EXAMPLE 4 (method a)

1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-4,4,5,5-tetra-deuteroimidazolidin-2-one, **4**.

N-(2-Benzylxyethyl)oxamide, **4a**.

15 A solution of 2-benzylxyethylamine (25 g) and potassium carbonate (50 g) in dichloromethane (500 ml) was treated dropwise with methyl chlorooxacetate (25 g) at 0 °C. After stirring for 3 h at room temperature, the mixture was washed with aq. sodium bicarbonate and dried over magnesium sulfate. Removal of solvent *in vacuo* gave methyl (2-benzylxyethyl)aminoxyacetate as an oil. Yield: 40 g.

20 The oil was dissolved in tetrahydrofuran, conc. aq. ammonia (500 ml) was added followed by reflux for 1/2 h. After cooling, the phases were separated, the aqueous phase was extracted with dichloromethane, and the combined organic phases were dried over magnesium sulfate. Removal of the solvent gave **4a** as a crystalline material. Yield: 32 g.

25

2-(2-Benzylxyethylamino)-1,1,2,2-tetradeuteroethylamine, **4b**

A suspension of lithium aluminium deuteride (20 g) in tetrahydrofuran (600 ml) was treated portionwise with **4a** (22 g). After reflux for 16 h the mixture was cooled and treated subsequently with water (40 ml), 15% sodium hydroxide (20 ml), and water (100 ml). The mixture was filtered and the precipitate extracted with dichloromethane (1000 ml). The filtrate was concentrated *in vacuo* and the remaining oil mixed with the dichloromethane phase. Drying over magnesium sulfate and removal of solvent *in vacuo* gave **4b** as a yellow oil. Yield: 19 g.

1-(2-Chloroethyl)-4,4,5,5-tetradeuteroimidazolidin-2-one, 4c.

A mixture of **4b** (19 g) and urea (7.5 g) was heated to 180 °C for 1 h. Purification by column chromatography (silica gel, eluent: methanol/ethyl acetate 1:4) gave 1-(2-benzyloxyethyl)-4,4,5,5-tetradeuteroimidazolidin-2-one as an oil. Yield: 13.2 g.

The oil was dissolved in ethanol (200 ml) and 5% Pd/C (3.5 g) was added. The mixture was treated with 4 atm. of hydrogen gas for 16 h. Filtration and removal of solvent gave 1-(2-hydroxyethyl)-4,4,5,5-tetradeuteroimidazolidin-2-one as an oil. Yield: 7.8 g.

10 The oil was suspended in dry toluene (50 ml). Thionyl chloride (7 ml) and dimethyl formamide (0.5 ml) was added followed by heating to 70 °C for 2 h. The mixture was concentrated *in vacuo*, brine was added followed by extraction with dichloromethane. Drying over magnesium sulfate and treatment with charcoal gave, after removal of solvent *in vacuo*, the title compound as a crystalline solid. Yield: 7.4 g.

15

1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-4,4,5,5-tetradeuteroimidazolidin-2-one, 4.

A mixture of 5-chloro-1-(4-fluorophenyl)-3-(4-piperidinyl)-1H-indole (12.5 g), **4c** (4.5 g), potassium carbonate (10 g), and potassium iodide (1 g) in isopropyl methyl ketone was kept at 95 °C for 16 h. The mixture was cooled, filtered, and concentrated *in vacuo*. Purification by column chromatography (silica gel, eluent: triethylamine/methanol/ethyl acetate 1:2:17) gave the title compound as a solid. Recrystallization from ethanol yielded 7.8 g of crystalline **4**. Mp.: 159-62 °C.

1H NMR (δ , CDCl₃): 7.64 (d, 1H), 7.45-7.28 (m, 3H), 7.24-7.09 (m, 3H), 7.08 (s, 1H), 5.13 (s, 1H), 3.38 (t, 2H), 3.12-3.01 (m, 2H), 2.89-2.72 (m, 1H), 2.57 (t, 2H), 2.28-2.13 (m, 2H), 2.11-1.98 (m, 2H), 1.90-1.69 (m, 2H).

EXAMPLE 5 (method a)

1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-4,4-dideutero-imidazolidin-2-one, **5**.

(2-Benzylxyethyl)aminoacetonitrile, 5a.

A mixture of 2-benzylxyethylamine (40 g) and triethylamine (50 ml) in tetrahydro-

furan (500 ml) was treated dropwise with chloroacetonitrile (23 g) at room temperature. After reflux for 2 h the mixture was cooled and filtered, water (400 ml) was added and the mixture was extracted with dichloromethane. The solvent was removed *in vacuo*, ether (400 ml) was added and the ether solution was treated 5 with magnesium sulfate and charcoal. Filtration and removal of solvent *in vacuo* gave 5a as a yellow oil. Yield: 39 g.

2-(2-Benzylxyethylamino)-1,1-dideuteroethylamine, 5b.

A suspension of lithium aluminium deuteride (15 g) in dry tetrahydrofuran (400 ml) 10 was treated portionwise under nitrogen gas with aluminium chloride (23 g) at room temperature. After stirring for 1/2 h, a solution of 5a (29 g) in tetrahydrofuran (50 ml) was added dropwise followed by reflux for 1 h. After cooling 15% sodium hydroxide (80 ml) was slowly added followed by addition of water (40 ml). The mixture was filtered and the precipitate extracted with dichloromethane (800 ml). The filtrate 15 from the filtration was concentrated *in vacuo* and the remaining oil mixed with the dichloromethane phase. Drying over magnesium sulfate and removal of solvent *in vacuo* gave a mixture of 5b and 2-benzylxyethylmethylamine, 22 g. The mixture was used directly in the next step.

20 **1-(2-Chloroethyl)-4,4-dideuteroimidazolidin-2-one, 5c.**

The mixture of 5b and 2-benzylxyethylmethylamine (22 g) and urea (7.5 g) was heated to 180 °C for 1 h. Purification by column chromatography (silica gel, eluent: triethylamine/methanol/ethyl acetate 5:2:93) gave 1-(2-benzylxyethyl)-4,4-dideuteroimidazolidin-2-one as an oil. Yield: 6.4 g. The oil was dissolved in ethanol (100 ml) and 5% Pd/C (1.5 g) was added. The mixture was treated with 4 atm. of hydrogen gas for 16 h. Filtration and removal of solvent gave 1-(2-hydroxyethyl)-25 4,4-dideuteroimidazolidin-2-one as an oil. Yield: 3.8 g. The oil was suspended in dry toluene (25 ml). Thionyl chloride (3.5 ml) and dimethyl formamide (0.1 ml) was added followed by heating to 70 °C for 2 h. The mixture was concentrated *in vacuo*, 30 brine was added followed by extraction with dichloromethane. Drying over magnesium sulfate, treatment with charcoal and removal of solvent *in vacuo*, gave the title compound as a crystalline solid. Yield: 4.1 g.

1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-4,4-dideuteroimidazolidin-2-one, 5.

This compound was prepared by a procedure analogous to the procedure described for the synthesis of 4 using **5c** as starting material. Mp.: 159-62 °C.

- 5 ^1H NMR (δ , CDCl_3): 7.64 (d, 1H), 7.45-7.28 (m, 3H), 7.24-7.09 (m, 3H), 7.08 (s, 1H), 4.45 (s, 1H), 3.56 (s, 2H), 3.38 (t, 2H), 3.12-3.01 (m, 2H), 2.89-2.72 (m, 1H), 2.57 (t, 2H), 2.28-2.13 (m, 2H), 2.11-1.98 (m, 2H), 1.90-1.69 (m, 2H).

EXAMPLE 6 (method a)

- 10 *1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-5,5-dideuteroimidazolidin-2-one, 6*

Azido-N-(2-benzyloxyethyl)acetamide, 6a

A solution of 2-benzyloxyethylamine (15 g) and potassium carbonate (40 g) in acetone (400 ml) was treated dropwise with azidoacetyl chloride at 20 °C. After stirring for 3 h at room temperature, the mixture was filtered and concentrated *in vacuo*. Dichloromethane (800 ml) was added, and the solution was washed with aq. sodium bicarbonate. The organic phase was dried over magnesium sulfate. Removal of solvent *in vacuo* gave a yellow oil which was filtered through silica gel with ethyl acetate. Removal of the solvent *in vacuo* gave **6a** as a colorless oil. Yield: 22 g.

2-(2-Benzylamino)-2,2-dideuteroethylamine, 6b

A suspension of lithium aluminium deuteride (10 g) in tetrahydrofuran (300 ml) was treated dropwise with a solution of **6a** (14 g) in tetrahydrofuran (50 ml). After reflux for 16 h, the mixture was cooled and subsequently treated with water (20 ml), 15% sodium hydroxide (10 ml), and water (50 ml). The mixture was filtered and the precipitate extracted with dichloromethane (600 ml). The filtrate was concentrated *in vacuo* and the remaining oil mixed with the dichloromethane phase. Drying over MgSO_4 and removal of solvent *in vacuo* gave **6b** as a yellow oil. Yield: 9.4 g.

30

1-(2-Chloroethyl)-5,5-dideuteroimidazolidin-2-one, 6c.

This compound was prepared by a procedure analogous to the procedure described for the synthesis of **4c** using **6b** as starting material.

1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-5,5-dideuteroimidazolidin-2-one, 6.

This compound was prepared by a procedure analogous to the procedure described for the synthesis of **4** using **6c** as starting material. Mp.: 160-62 °C. 1H NMR (δ , CDCl₃): 7.64 (d, 1H), 7.45-7.28 (m, 3H), 7.24-7.09 (m, 3H), 7.08 (s, 1H), 4.78 (s, 1H), 3.41 (s, 2H), 3.38 (t, 2H), 3.12-3.01 (m, 2H), 2.89-2.72 (m, 1H), 2.57 (t, 2H), 2.28-2.13 (m, 2H), 2.11-1.98 (m, 2H), 1.90-1.69 (m, 2H).

10 EXAMPLE 7 (method c)

1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-4-hydroxyimidazolidin-2,5-dione, 7a and *1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-5-hydroxyimidazolidin-2,4-dione, 7b.*

15 *5-Chloro-1-(4-fluorophenyl)-3-[1-(2-ureidoethyl)piperidin-4-yl]-1H-indol, 7c.*

Potassium cyanate (4.9 g) was suspended in dichloromethane (50 ml) followed by dropwise addition of trifluoroacetic acid (4.4 ml) at 0 °C. A solution of 3-[1-(2-aminoethyl)piperidin-4-yl]-5-chloro-1-(4-fluorophenyl)-1H-indol (10.8 g) (Pat. Appl. No. WO 9215302, Chem. Abstr. 117 (1992) 247029) in dichloromethane (100 ml) was added dropwise followed by stirring for 6 h at room temperature. Water (100 ml) was added and the reaction mixture made alkaline with conc. ammonia. The phases were separated followed by extraction with dichloromethane. The combined organic phases were dried over magnesium sulfate. Removal of solvent *in vacuo* gave a heavy oil which was purified by flash chromatography (silica gel, eluent: triethylamine/methanol/ethyl acetate 5:20:75). The title compound was isolated as a crystalline material, mp. 161-63 °C. Yield: 7.9 g.

1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-4-hydroxyimidazolidin-2,5-dione, 7a, and *1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-5-hydroxyimidazolidin-2,4-dione, 7b.*

A mixture of **7c** (1.6 g) and glyoxylic acid monohydrate (0.5 g) in 80% acetic acid (25 ml) was refluxed for 1 h. The reaction mixture was concentrated *in vacuo* followed by addition of saturated aq. sodium bicarbonate solution (100 ml).

Extraction with dichloromethane, drying of the organic phase over magnesium sulfate and removal of solvent *in vacuo* gave a heavy oil which was separated by flash chromatography (silica gel, triethylamine/methanol/ethyl acetate 5:2:93).

Fraction 1: crystalline **7a**, mp. 128-35 °C. Yield: 0.2 g. ¹H NMR (δ , CDCl₃): 7.59 (d, 5 1H), 7.45-7.28 (m, 3H), 7.24-7.08 (m, 4H), 5.35 (s, 1H), 3.71-3.56 (m, 2H), 3.40-3.22 (m, 2H), 3.00-2.54 (m, 3H), 2.32-1.71 (m, 6H).

Fraction 2: crystalline **7b**, mp 172-80 °C. Yield: 0.35 g. ¹H NMR (δ , CDCl₃): 7.59 (d, 10 1H), 7.48-7.29 (m, 3H), 7.28-7.12 (m, 3H), 7.09 (s, 1H), 5.09 (s, 1H), 4.20-4.06 (m, 1H), 3.37-3.01 (m, 3H), 3.00-2.82 (m, 1H), 2.81-2.63 (m, 1H), 2.61-2.42 (m, 2H), 2.32-2.04 (m, 3H), 1.98-1.74 (m, 2H).

EXAMPLE 8 (method a)

1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidin-1-yl]ethyl]-4,4-dimethylimidazolidin-2-one. **8**.

15

2-(2-Benzylxyethylamino)-1,1-dimethylethylamine, 8a.

To a mixture of 2-bromo-2-methylpropionylbromid (76 g), K₂CO₃ (55 g) and dichloromethane (700 ml) was added a solution of 2-benzylxyethylamine (50 g) in dichloromethane (500 ml) at -10 °C. After stirring at room temperature for 1.5 h the mixture was washed with water (500 ml) and dried (MgSO₄). Evaporation of the solvents *in vacuo* afforded *N*-(2-benzylxyethyl)-2-bromo-2-methylpropionamide as an oil: 104 g

A mixture of the crude amide (104 g), sodium azide (23.6 g) and *N*-methyl-2-pyrrolidone (500 ml) was heated at 50 °C for 22 h. After cooling to room temperatur 25 water was added and the resulting mixture was extracted with diethyl ether (2 X 400 ml). The combined organic phases were washed with brine (3 X 500 ml) and dried (Na₂SO₄). Evaporation of the solvents *in vacuo* gave 2-azido-*N*-(2-benzylxyethyl)-2-methylpropionamide as an oil:78 g.

A solution of 2-azido-*N*-(2-Benzylxyethyl)-2-methylpropionamide (70 g) in THF 30 (750 ml) was added to a suspension of LiAlH₄ (20 g) in THF (500 ml) at 0 °C during 1 h. After reflux for 4 h, the mixture was cooled to 0 °C, water (20 ml) and aqueous NaOH (20 ml) were added, the inorganic salts were filtered off and the solvents were dried. Evaporation of the solvents *in vacuo* gave **8a** as an oil: 53 g.

1-(2-Chloroethyl)-4,4-dimethylimidazolidin-2-one, 8b.

This compound was prepared by a procedure analogous to the procedure described for the synthesis of 4c using 8a as starting material.

5

1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-4,4-dimethylimidazolidin-2-one, 8.

This compound was prepared by a procedure analogous to the procedure described for the synthesis of 4 using 8b as starting material: mp 142-144 °C;

- 10 ^1H NMR (CDCl_3) δ 7.65 (d, 1H), 7.45-7.30 (m, 3H), 7.25-7.10 (m, 3H), 7.05 (s, 1H),
4.40 (s, 1H), 3.35 (t, 2H), 3.25 (s, 2H), 3.15-3.00 (m, 2H), 2.90-2.70 (m, 1H), 2.60
(t, 2H), 2.30-2.15 (m, 2H), 2.15-2.00, 1.90-1.70 (m, 2H), 1.30 (s, 6H).

EXAMPLE 9 (method a)

- 15 1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-5,5-dimethylimidazolidin-2-one, 9.

1-(2-Benzylxyethyl)-5,5-dimethylimidazolidin-2,4-dione, 9a.

- A mixture of 2-benzylxyethylamine (50 g), ethyl 2-bromo-2-methylpropionate (97.5
20 g) and *N*-methyl-2-pyrrolidone (1l) was heated at 100 °C for 7 h. The mixture was
cooled to room temperature, water was added and the resulting mixture was
extracted with ethyl acetate (2 X 500 ml). The combined organic phases were
washed with water (4 X 500 ml) and brine (2 X 500 ml), dried (Na_2SO_4) and the
solvents were evaporated *in vacuo*. Purification of the remaining oil by column
25 chromatography on silica gel (ethyl acetat containing 4% triethylamine) gave ethyl
2-(2-benzylxyethylamino)-2-methylpropionate as an oil: 30 g

- A mixture of ethyl 2-(2-benzylxyethylamino)-2-methylpropionate (29 g) and urea
(8.5 g) was heated at 180 °C for 1 h. After cooling to room temperature water (250
ml) was added and the resulting mixture was extracted with diethyl ether (500 ml).
30 The organic phase was washed with brine (400 ml) and dried (Na_2SO_4). Evaporation
of the solvents *in vacuo* afforded 9a as an oil: 28 g.

1-(2-Benzylxyethyl)-5,5-dimethylimidazolidin-2-one, 9b.

A solution of **9a** (28 g) in THF (250 ml) was added to a suspension of LiAlH₄ (8 g) in THF (250 ml) at 20-25 °C. After stirring at room temperature for 1 h, the mixture was cooled to 0 °C, water (10 ml) and aqueous NaOH (10 ml) were added, the inorganic salts were filtered and the solvents were evaporated *in vacuo*. The remaining oil was purified by column chromatography on silica gel (ethyl acetate) yielding **9b** as an oil: 10 g.

1-(2-Chloroethyl)-5,5-dimethylimidazolidin-2-one, 9c.

10 **9b** (9 g) was dissolved in ethanol (150 ml) and 5% Pd/C (2.0 g) was added. The mixture was treated with 3 atm. of H₂ gas for 36 h. Filtration and removal of solvent gave 1-(2-hydroxyethyl)-5,5-dimethylimidazolidin-2-one as an oil. Yield: 5.1g. The oil was suspended in dry toluene (50 ml). Thionyl chloride (5 ml) and dimethyl formamide (0.5 ml) were added followed by heating to 70 °C for 2 h. The mixture **15** was concentrated *in vacuo*, brine (100 ml) was added followed by extraction with dichloromethane (100 ml). The organic phase was dried (MgSO₄) and the solvents evaporated *in vacuo* affording the title compound as an oil. Yield: 5 g.

1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-5,5-dimethyl-

20 imidazolidin-2-one, 9.

This compound was prepared by a procedure analogous to the procedure described for the synthesis of **4** using **9c** as starting material. mp 146-148 °C; **1H NMR** (CDCl₃) δ 7.65 (d, 1H), 7.45-7.30 (m, 3H), 7.25-7.10 (m, 3H), 7.05 (s, 1H), 4.70 (s, 1H), 3.25 (t, 2H), 3.15 (s, 2H), 3.20-3.05 (m, 2H), 2.90-2.70 (m, 1H), 2.60 **25** (t, 2H), 2.35-2.20 (m, 2H), 2.15-2.00 (m, 2H), 1.95-1.70 (m, 2H), 1.30 (s, 6H).

EXAMPLE 10 (method f)

1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-5,5-dimethylimidazolidin-2,4-dione, 10.

30

This compound was prepared by a procedure analogous to the procedure described for the synthesis of **9a** using 2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethylamine (prepared as described for similar compounds in

J.Med.Chem. **1992**, *35*, 4813-4822) as starting material. The compound was precipitated as its triethylammonium salt from ethyl acetate. mp 140-142 °C 1H NMR (CDCl_3) δ 7.65 (d, 1H), 7.45-7.30 (m, 3H), 7.25-7.10 (m, 3H), 7.05 (s, 1H), 3.65 (q, 6H), 3.45 (t, 2H), 3.20-3.05 (m, 2H), 2.90-2.80 (m, 1H), 2.70 (t, 2H), 2.40-5 2.20 (m, 2H), 2.15-2.00 (m, 2H), 1.95-1.70 (m, 2H), 1.50 (t, 9 H), 1.45 (s, 6H).

EXAMPLE 11 (method b)

1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidin-1-yl]ethyl]-4,5-dihydroxy-imidazolidin-2-one, **11**

10

A solution of **7a** (0.5 g) in tetrahydrofuran (25 ml) was cooled to 0 °C and treated portionwise with LiAlH₄ (15 mg) while strictly keeping the temperature at 0 °C. After stirring for 2 h at 0 °C additional LiAlH₄ (15 mg) was added portionwise followed by stirring for 2 h at 0 °C. The reaction was quenched with water/aq. 4 N NaOH followed by removal of solvent *in vacuo*. Methylene chloride (25 ml) was added and the resulting solution dried over MgSO₄ and concentrated *in vacuo*. The remaining oil was purified by flash chromatography (silica gel, eluent: ethyl acetate/methanol/triethylamine 85:10:5). The title compound was obtained as a crystalline material, mp. 190-92 °C. Yield: 74 mg. 1H NMR ($\text{DMSO}-d_6$) δ 7.70 (d, 1H), 7.65-7.50 (m, 2H), 7.50-7.30 (m, 4H), 7.15 (t, 1H), 4.65 (s, 1H), 4.60 (s, 1H), 3.55-3.05 (m, 3H), 3.00-20 2.70 (m, 2H), 2.60-2.20 (m, 3H), 2.20-1.85 (m, 3H), 1.85-1.60 (m, 2H).

EXAMPLE 12

3-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidin-1-yl]ethyl]-1,3-diazaspiro[4.4]nonan-2-one, **12**.

*1-Azido-N-(2-benzyloxyethyl)cyclopentan-1-carboxamide, **12a**.*

1-Azidocyclopentan-1-carbonylchloride (16.8 g) was added to a mixture of 2-benzyloxyethylamine (14.7 g), K₂CO₃ (16.6 g) and acetone at 0 °C. After stirring at room temperature for 2 h the mixture was filtered, concentrated *in vacuo* and after addition water (100 ml) extracted with diethyl ether (2 X 100 ml). The combined organic phases were washed with brine and dried (Na₂SO₄). Evaporation of the solvents gave the crude **12a** as an oil: 22.3 g.

1-(2-benzyloxyethylaminomethyl)cyclopentylamine, 12b.

A solution of the crude 1-azido-N-(2-benzyloxyethyl)cyclopentan-1-carboxamide 12a (22.3 g) in tetrahydrofuran (100 ml) was added to a suspension of LiAlH₄ (6 g) in tetrahydrofuran (100 ml). After reflux for 2 h the mixture was cooled to 0 °C and subsequently treated with water (6 ml), 15 % aqueous NaOH (6 ml) and water (6 ml). The mixture was filtered and the precipitate extracted with dichloromethane (200 ml). Drying of the combined organic phases (MgSO₄) and evaporation of the solvents *in vacuo* afforded the title compound as an oil: 18.7 g.

10

3-(2-chloroethyl)-1,3-diazaspiro[4.4]nonan-2-one, 12c.

This compound was prepared by a procedure analogous to the procedure described for the synthesis of 4c using 12b as starting material.

15 *3-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-1,3-diazaspiro[4.4]nonan-2-one, 12d.*

This compound was prepared by a procedure analogous to the procedure described for the synthesis of 4 using 12c as starting material: mp 176-178 °C;

20 ¹H NMR (CDCl₃) δ 7.65 (d, 1 H), 7.45-7.30 (m, 3 H), 7.25-7.10 (m, 3 H), 7.05 (s, 1 H), 4.75 (s, 1 H), 3.40-3.30 (m, 4 H), 3.15-3.00 (m, 2 H), 2.90-2.70 (m, 1 H), 2.55 (t, 2 H), 2.30-2.15 (m, 2 H), 2.15-1.95 (m, 2 H), 1.90-1.55 (m, 10 H).

EXAMPLE 13

25 *1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-1,3-diazaspiro[4.4]nonan-2-one, 13.*

1-(2-Benzylacetamido)-cyclopentyl-1-carboxamide, 13a

Benzylacetylchloride (16.7 g) was added to a mixture of 1-aminocyclopentan-1-carboxamide (10.2 g), K₂CO₃ (13.3 g) and acetone (150 ml) at -5 to 0 °C. After stirring at room temperature for 2 h the reaction mixture was filtered. The precipitate was extracted with diethyl ether (50 ml) washed with water (100 ml) and dried at 50 °C *in vacuo* for 18 h giving the title compound as a crystalline material: 13.8 g.

N-(1-aminomethylcyclopentyl)-N-(2-Benzylxyethyl)amine, 13b.

This compound was prepared by a procedure analogous to the procedure described for the synthesis of **12b** using **13a** as starting material.

5 ***1-(2-Chloroethyl)-1,3-diazaspiro[4.4]nonan-2-one, 13c.***

This compound was prepared by a procedure analogous to the procedure described for the synthesis of **4c** using **13b** as starting material.

10 ***1-[2-[4-{5-Chloro-1-(4-fluorophenyl)-1H-indol-3-yl]piperidin-1-yl]ethyl]-1,3-diazaspiro-[4.4]nonan-2-one, 13.***

This compound was prepared by a procedure analogous to the procedure described for the synthesis of **4** using **13c** as starting material: mp 143-145 °C; ¹H NMR (CDCl₃) δ 7.65 (d, 1 H), 7.45-7.30 (m, 3 H), 7.25-7.10 (m, 3 H), 7.05 (s, 1 H), 4.65 (s, 1 H), 3.30-3.15 (m, 4 H), 3.15-3.05 (m, 2 H), 2.90-2.75 (m, 1 H), 2.60 (t, 15 2 H), 2.35-2.20 (m, 2 H), 2.10-2.00 (m, 2 H), 1.95-1.50 (m, 10 H).

Pharmacology

The compounds used in the invention were tested in accordance with the following 20 well recognized and reliable test methods.

Inhibition of ³H-Ketanserin Binding To 5-HT₂ Receptors in Rat Cortex *in vitro*.

By this method the inhibition by drugs of the binding of ³H-Ketanserin (0,5 nM) to 5-HT₂ receptors in membranes from rat is determined *in vitro*. The method is 25 described in Hyttel, *Pharmacology & Toxicology* **61**, 126-129, 1987. The results are shown in Table 1.

Inhibition of ³H-Spiperone Binding to Dopamine D₂ Receptors in Rat Corpus Striatum *in vitro*

30 By this method the inhibition by drugs of the binding of ³H-spiperone (0.5 nM) to dopamine D₂ receptors in membranes from rat corpus striatum is determined *in vitro*. The method and results for standard compounds are described in Hyttel & Larsen, *J. Neurochem*, **44**, 1615-1622, 1985). The results are shown in Table 1.

Quipazine Inhibition

Quipazine is a 5-HT₂ agonist, which induces head twitches in rats. The test is an *in vivo* test for 5-HT₂-antagonistic effect measuring the ability to inhibit quipazine induced head twitches. The method and test results for some reference substances are published by Arnt et al. (*Drug Development Research*, **16**, 59-70, 1989, attached). The results are shown in Table 2.

Catalepsy

- 10 Evaluation of catalepsy is made according to Arnt (*Eur. J. Pharmacol.* **90**, 47 -55 (1983)). Test compound is given s.c. in different doses. The rat (170 - 240 g) is placed on a vertical wire mesh (mesh diameter 12 mm). The rat is considered cataleptogenic if it remains immobile for more than 15 sec. The maximum number of rats showing catalepsy within the first 6 hours is recorded for each dose group.
- 15 The results are recorded in fractions and an ED₅₀ value is calculated by means of log-probit analysis. The results are shown in Table 2.

Table 1: RECEPTOR BINDING DATA (IC₅₀ values in nM)

Compound No.	5-HT ₂ binding [³ H]-ketanserin	Dopamine D ₂ binding [³ H]-spiroperidol
20		
1	1.4	5.5
3	1.5	13
25	4	8.3
5	0.69	5.9
6	0.98	7.6
7a	6.6	18
7b	9.8	23
30	8	18
9	1.7	14
10	12	20
11	2.5	18
12	4.7	19
35	13	30
	sertindole	4.1

Table 2: IN VIVO ACTIVITY (ED₅₀ values in µmol/kg)

	Compound No	Quipazine inhibition		Catalepsy
		2 hours (sc)	24 hours (po)	
5	1	0.099	0.085	39
	3			17
	4	0.070	<0.0056	>45
10	5	0.055	0.0097	>45
	6	0.020	0.012	30
	7a			>42
	7b			>21
	8	0.035	0.013	>43
15	9	0.13	0.078	>43
	10	0.33		>30
	12	0.076	0.037	>40
	13	0.088	0.45	>40
	sertindole	0.035	0.039	>91
20				

Some of the compounds of the invention have also been found to inhibit the firing of spontaneously active DA neurones in the *ventral tegmental* area of the brain upon 21 days of repeated oral treatment of rats. The test which was performed 25 according to the method described by Skarsfeldt, T. and Perregaaard, J., Eur. J. Pharmacol. 1990, 182, 613-614 is indicative of antipsychotic effects in humans.

Results

30 It appears from Table 1 that, like sertindole, the compounds of the invention have affinity for the serotonin 5-HT₂ receptor and the dopamine D₂ receptor, respectively. Furthermore, it is seen from the *in vivo* test data in Table 2 that the compounds are substantially non-cataleptogenic, potent and long-lasting 5-HT₂ antagonists *in vivo*.

35

Formulation Examples

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art.

For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: corn starch, lactose, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any 5 other adjuvant or additive colourings, aroma, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by solving the active ingredient and possible additives in a part of the vehicle, preferably sterile water, adjusting the 10 solution to the desired volume, sterilization of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Typical examples of recipes for the formulations of the invention are as follows:

15

1) Tablets containing 5 milligrams of Compound **6** calculated as the free base:

Compound 6	5.0 mg
Lactose	60 mg
Maize starch	30 mg
20 Hydroxypropylcellulose	2.4 mg
Microcrystalline cellulose	19.2 mg
Croscarmellose Sodium Type A	2.4 mg
Magnesium stearate	0.84 mg

25

2) Tablets containing 1 milligram of Compound **8** calculated as the free base:

Compound 8	1.0 mg
Lactose	46.9 mg
Maize starch	23.5 mg
Povidone	1.8 mg
30 Microcrystalline cellulose	14.4 mg
Croscarmellose Sodium Type A	1.8 mg
Magnesium stearate	0.63 mg

3) Syrup containing per millilitre:

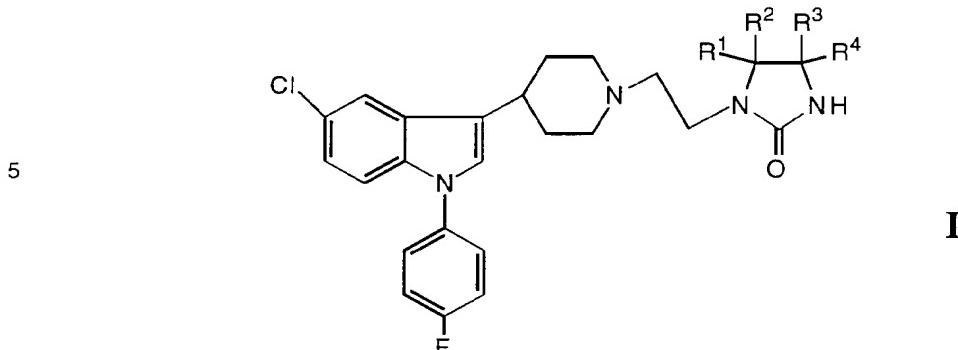
	Compound 4	5.0 mg
	Sorbitol	500 mg
	Hydroxypropylcellulose	15 mg
5	Glycerol	50 mg
	Methyl-paraben	1 mg
	Propyl-paraben	0.1 mg
	Ethanol	0.005 ml
	Flavour	0.05 mg
10	Saccharin sodium	0.5 mg
	Water	ad 1 ml

4) Solution for injection containing per millilitre:

	Compound 6	0.5 mg
15	Sorbitol	5.1 mg
	Acetic acid	0.08 mg
	Water for injection	ad 1 ml

CLAIMS

1. A phenylindole compound having general formula I



wherein R¹ - R⁴ are independently selected from the group consisting of hydrogen, deuterium, halogen, C₁₋₆ alkyl, cycloalkyl, cycloalkyl-C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, aryl, hydroxy, C₁₋₆ alkoxy, cycloalkyloxy, cycloalkyl-C₁₋₆ alkyloxy, aryl-C₁₋₆ alkyloxy, 10 aryloxy, C₁₋₆ alkylthio, cycloalkylthio, cycloalkyl-C₁₋₆ alkylthio, aryl-C₁₋₆ alkylthio and arylthio, with the proviso that all 4 substituents cannot be hydrogen; or
 at least one pair of substituents (R¹,R² or R³,R⁴) constitutes an oxo group or a thioxo group and, if only one oxo or thioxo group is present, the other two substituents are selected from the above group defined for R¹ - R⁴, with the proviso that
 15 they may not both be hydrogen; or
 R¹ and R² and/or R³ and R⁴, respectively, are joined together to form a 3-8 membered spiro ring optionally containing one oxygen or sulfur atom in the ring; or a prodrug or acid addition salt thereof.

20

2. A compound of Claim 1, characterised in that R¹ - R⁴ are individually selected from the group consisting of hydrogen, deuterium, lower alkyl, hydroxy and lower alkoxy; or
 one or both pair of substituents (R¹,R² or R³,R⁴) constitute an oxo group or are
 25 joined together to form a 3-8 membered spiro ring.

3. A compound of Claim 1, **characterised in** that both substituents of at least one pair of substituents (R₁,R₂ or R₃,R₄) are both different from hydrogen or constitute together an oxo group or are joined to form a spiro ring.

5

4. A pharmaceutical composition, **characterised in** that it comprises a compound of any of Claims 1 - 3 together with a pharmaceutically acceptable carrier or diluent.

10

5. Use of a compound of any of Claims 1 - 3 for preparing a pharmaceutical composition for treatment of psychosis, depression, negative symptoms of schizophrenia, hypertension or extrapyramidal side effects induced by antipsychotic drugs.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 94/00407

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/14, A61K 31/445
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A1, 9200070 (H. LUNDBECK A/S), 9 January 1992 (09.01.92), see especially page 9 line 20 --	1-5
A	EP, A2, 0392959 (H. LUNDBECK A/S), 17 October 1990 (17.10.90) --	1-5
A	EP, A1, 0200322 (H. LUNDBECK A/S), 5 November 1986 (05.11.86) -- -----	1-5

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	
"A"	document defining the general state of the art which is not considered to be of particular relevance
"B"	earlier document but published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

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Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. + 46 8 666 02 86

Authorized officer

Göran Karlsson
Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT
Information on patent family members

31/12/94

Int'l. application No.
PCT/DK 94/00407

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